

We claim:

1. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the amino acid sequence  $X_1X_2X_3X_4X_5$ , wherein  $X_1$ ,  $X_2$ ,  
5  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  is any polar amino acid.
2. The method according to claim 1 wherein  $X_1$ ,  $X_2$ , and  $X_5$  are selected from the group consisting of phenylalanine and tyrosine,  $X_3$  is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and  $X_4$  is selected from group consisting of tryptophan, tyrosine and phenylalanine.
- 10 3. The method according to claim 2 wherein said amino acid sequence is an insulin agonist.
4. The method according to claim 2 wherein said amino acid sequence is an insulin antagonist.
- 15 5. The method according to claim either one of claims 3 or 4 wherein  $X_1$  and  $X_5$  are phenylalanine and  $X_2$  is tyrosine.
6. The method according to claim 5 wherein  $X_4$  is tryptophan.
7. The method according to claim 6 wherein the amino acid sequence is an insulin agonist and  $X_3$  is selected from the group consisting of aspartic acid and glutamic acid.
- 20 8. The method according to claim 7 wherein  $X_3$  is aspartic acid to result in an amino acid sequence comprising FYDWF.

9. The method according to claim 7 wherein  $X_3$  is glutamic acid to result in an amino acid sequence comprising FYEWF.

10. The method according to claim 1 wherein the amino acid sequence FHEN is bound to the amino terminal of  $X_1X_2X_3X_4X_5$  to produce an amino acid sequence comprising FHEN $X_1X_2X_3X_4X_5$  and possessing insulin agonist activity.

5 11. The method according to claim 10 wherein the amino acid sequence is FHENFYDWF.

12. The method according to claim 1 wherein the amino acid sequence  $X_1X_2X_3X_4X_5$  further comprises the amino acid sequence  $X_{93} X_{94} X_{95} X_{96} X_{97}$  located at the carboxy terminal end adjacent to  $X_5$ , wherein  $X_{93}$ ,  $X_{94}$  and  $X_{97}$  may be any amino acid,  $X_{95}$  is selected from the group consisting of glutamine, glutamic acid, alanine and lysine, and  $X_{96}$  is a hydrophobic or aliphatic amino acid.

10 13. The method according to claim 12 wherein  $X_{93}$  is selected from the group consisting of alanine, aspartic acid, glutamic acid, arginine, and valine,  $X_{95}$  is glutamine or glutamic acid, and  $X_{96}$  is selected from the group consisting of leucine, isoleucine, valine and tryptophan.

15 14. The method according to claim 13 wherein  $X_{96}$  is leucine or tryptophan.

20 15. The method according to claim 14 wherein  $X_{96}$  is leucine.

16. The method according to claim 13 wherein  $X_{95}$  is glutamine or glutamic acid, and  $X_{96}$  is tryptophan.

17. The method according to claim 13 wherein X<sub>95</sub> is glutamic acid and the  
amino acid sequence is an insulin agonist.

18. The method according to claim 13 wherein asparagine is present as the  
amino acid bound to the amino terminal of X<sub>1</sub> and wherein X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub>X<sub>93</sub>  
5 is FYDWFV

19. The method according to claim 1 wherein the amino acid sequence is  
selected from the group of amino acid sequences listed in Figures 1, 2, and  
9.

20. The method according to claim 1 wherein the sequence is selected from the  
group consisting of FHENFYDWFVRQVSK,  
10 DYKDVTFTSAVFHENFYDWFVRQVSKK,  
GRVDWLQRNANFYDWFVAELG and APTFYAWFNQQT.

21. The method according to claim 1 wherein the sequence is selected from the  
group consisting of  
15 FHENFYDWFVRQVAKK-NH<sub>2</sub>  
FHENFYDWFVRQASKK-NH<sub>2</sub>  
FHENFYDWFVRAVSKK-NH<sub>2</sub>  
FHENFYDWFVAQVSKK-NH<sub>2</sub>  
FHENFYDWFARQVSKK-NH<sub>2</sub>  
20 FHEAFYDWFVRQVSKK-NH<sub>2</sub>  
FHANFYDWFVRQVSKK-NH<sub>2</sub>  
FAENFYDWFVRQVSKK-NH<sub>2</sub>  
AHENFYDWFVRQVSKK-NH<sub>2</sub>  
phenfydwfvrvqskk  
25 EFHENFYDWFVRQVSEE  
FHENFYGWFVRQVSKK  
HETFYSMIRSLAK  
SDGFYNAIELLS  
SLENFYDALQLLAKK  
30 HDPFYSMMKSLLK

NSFYEALRMLSSK  
HPTSK~~E~~IYAKLLK  
HPSTNQMLM~~K~~LFK  
HPPLSELKLF~~L~~IKK  
5 HAPLSVLVQALLKK  
HPSLSDMRWILLK  
WSDFYSYFQGLD  
D117-Dap(D117)  
SSNFYQALM~~L~~LS  
10 D117-Dap(CO-CH<sub>2</sub>-O-NH<sub>2</sub>)  
HENFYGW~~F~~VRQVSKK  
D117-Lys(D117)  
D117-b-Ala-Lys(D117)  
D117-b-Ala-Dap(b-Ala-D117)  
15 D117-Gly-Lys(Gly-D117)  
D117-b-Ala-Lys(b-Ala-D117)  
D117-Dab(D117)  
D117-Orn(D117)  
D117-Dap(b-Ala-D117)  
20 D117-b-Ala-Orn(b-Ala-D117)  
1-(Thia-b-Ala-D117)<sub>2</sub>  
FHENFYDW~~F~~VRQVS  
FHENFYDW~~F~~VRQVSK  
FHENFYDW~~F~~VQVSK  
25 FHENFYDW~~F~~VVSK  
FHENFYDW~~F~~VSK  
FHENFYDW~~F~~V~~K~~  
FYDW~~F~~-NH<sub>2</sub>  
FYDW~~F~~KK-NH<sub>2</sub>  
30 AFYDWFAKK-NH<sub>2</sub>  
AAAAFYDW~~F~~AAAAAKK-NH<sub>2</sub>  
(D117)<sub>2</sub>-12  
(Cys-Gly-D117)<sub>2</sub>  
Cys-Gly-D117  
35 (D117)<sub>2</sub>-14  
LDALDRLMRYFEERPSL-NH<sub>2</sub>  
PLAELWAYFEHSEQGRSSAH-NH<sub>2</sub>  
GRVDWLQRNANFYDW~~F~~V~~A~~ELG-NH<sub>2</sub>  
NGVERAGTGDNFYDW~~F~~V~~A~~QLH-NH<sub>2</sub>  
40 EHWNTVDPFYFTLFEWLRESG-NH<sub>2</sub>  
EHWNTVDPFYQYFSELLRESG-NH<sub>2</sub>  
QSDSGTVHDRFYGWFRDTWAS-NH<sub>2</sub>  
AFYDWFAK-NH<sub>2</sub>

AFYDWFA-NH<sub>2</sub>  
AFYDWF-NH<sub>2</sub>  
FYDWDA-NH<sub>2</sub>  
Ac-FYDWF-NH<sub>2</sub>  
5 Lig-FHENFYDWFVRQVSKK  
Lig-GGGFHENFYDWFVRQVSKK  
FHENFYDWFVRQVSKKGGG-Lig  
Lig-CAWPTYWNCG  
ACAWPTYWNCG-Lig  
10 ACAWPTYWNCGGGG-Lig  
Lig-SDGFYNAIELLS  
SDGFYNAIELLS-Lig  
SDGFYNAIELLSGGG-Lig  
15 KHLCVLEELFWGASLFGYCSGKK-Lig  
AFYDWFAKK-Lig  
AFYEWFAKK-NH<sub>2</sub>  
AFYGWFAKK-NH<sub>2</sub>  
AFYKWFAKK-NH<sub>2</sub>  
(SDGFYNAIELLS-Lig)<sub>2</sub>-14  
20 (AFYDWFAKK-Lig)<sub>2</sub>-14  
FHENAYDWFVRQVSKK  
FHENFADWFVRQVSKK  
FHENFYAWFVRQVSKK  
FHENFYDAFVRQVSKK  
25 FHENFTDWA VRQVSKK  
FQLLLEELVWGAPLFRYGTG  
PLCVLEELFWGASLFGQCSG  
QLEEEWAGVQCEVYGRECPS  
Cys-(Gly)<sub>2</sub>-D117  
30 (Cys-(Gly)<sub>2</sub>-D117)<sub>2</sub>  
(S210)-14-(S212)  
(S131)-14-(S212)  
(S205)<sub>2</sub>-14  
(S204)<sub>2</sub>-14  
35 (S131)-14-(S210)  
RVDWLQRNANFYDWFVAELG  
VDWLQRNANFYDWFVAELG  
DWLQRNANFYDWFVAELG  
WLQRNANFYDWFVAELG  
40 LQRNANFYDWFVAELG  
QRNANFYDWFVAELG  
RNANFYDWFVAELG  
NANFYDWFVAELG

ANFYDWFVAELG  
NFYDWFVAELG  
GRVDWLQRNANFYDWFVAELG-Lig  
Lig-GRVDWLQRNANFYDWFVAELG  
5 (S208)-14-(S131)  
(S208)-14-(S209)  
GRVDWLQRNANFYDWFVAEL  
GRVDWLQRNANFYDWFVAE  
GRVDWLQRNANFYDWFVA  
10 GRVDWLQRNANFYDWFV  
14-(SDGFYNAIELLS-Lig)<sub>2</sub>  
(GRVDWLQRNANFYDWFVAELG)-14  
14-(GRVDWLQRNANFYDWFVAE LG)  
(SDGFYNAIELLSGGG)<sub>2</sub>-14  
15 H-Acy-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub>  
RWPNFYGYFESLLTHFS-NH<sub>2</sub>  
HYNAFYEYFQVILLAETW-NH<sub>2</sub>  
EGWDFYSYFSGLLASVT-NH<sub>2</sub>  
LDRQFYRYFQDLLVGFM-NH<sub>2</sub>  
20 WGRSFYRYFETLLAQGI-NH<sub>2</sub>  
PLCFLQELFGGASLGGYCSG-NH<sub>2</sub>  
WLEQERAWIWCEIQGSGCRA-NH<sub>2</sub>  
IQGWEPTYGWFDDVVAQMFEET-NH<sub>2</sub>  
TGHRLGLDEQFYWWFRDALSG-NH<sub>2</sub>  
25 H-Abu-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub>  
14-(Dap-CAWPTYWNCG)<sub>2</sub>  
RDHypFYDWFDDi-NH<sub>2</sub>  
S131-14-S209  
S294-14-S210  
30 S295-14-S210  
S294-14-204  
S295-14-S204  
GFREGQRWYWFVAQVT-NH<sub>2</sub>  
VASGHVLHGQFYRWFVDQFALEE-NH<sub>2</sub>  
35 VGDFCVSHDCFYGWFLRESMQ-NH<sub>2</sub>  
DLRVLCELFGGAYVLGYCSE-NH<sub>2</sub>  
HLSVGEELSWWVALLGQWAR-NH<sub>2</sub>  
APVSTEELRWGALLFGQWAG-NH<sub>2</sub>  
AЛЕЕЕWA WVQVRSIRSGPL-NH<sub>2</sub>  
40 WLEHEWAQIQCЕLYGRGCTY-NH<sub>2</sub>  
AAVHEQFYDWFADQYEE-NH<sub>2</sub>  
QAPSNFYDWFVREWDEE-NH<sub>2</sub>  
QSFYDYIEELLGGEWKK-NH<sub>2</sub>

DPFYQGLWEWLRESGEE-NH<sub>2</sub>  
(S204)<sub>2</sub>7  
(S204)<sub>2</sub>9  
5 (S204)<sub>2</sub>12  
(S204)<sub>2</sub>13  
DWLQRNANFYDWFVAEL-Lig  
Lig-DWLQRNANFYDWFVAEL  
(S209)<sub>2</sub>9  
(S210)<sub>2</sub>9  
10 LigKHLCVLEELFWGASLFGYCSGKKKK  
KHLCVLEELFWGASLFGYCSGKKKK-Lig  
(S294)<sub>2</sub>14  
(S295)<sub>2</sub>14  
15 S-D-G-F-Y-N-A-Acy-E-L-L-S  
S-G-P-F-Y-E-E-Acy-E-L-L-W-Aib  
G-G-S-F-Y-D-D-Acy-E-Aib-L-W-Aib  
N-Aib-P-F-Y-D-E-Acy-D-E-Cha-W-Aib  
GRVDWLQRNANFYDWFVAEAcG-NH<sub>2</sub>  
and wherein underlined numbers represent a linker as defined in Table 18.

20 22. The method according to claim 2 wherein the amino acid sequence binds to the insulin receptor with an affinity of at least about 10<sup>-5</sup> M.

23. The method according to claim 22 wherein the affinity is at least about 10<sup>-7</sup> M.

24. The method according to claim 23 wherein the affinity is at least about 10<sup>-9</sup>

25 M.

26. The amino acid sequence according to claim 25 wherein the IGF-1R binding occurs with an affinity (K<sub>d</sub>) of at least about 10<sup>-5</sup> M.

27. The amino acid sequence according to claim 25 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-7}$  M.
28. The amino acid sequence according to claim 25 wherein  $X_1$ ,  $X_2$ , and  $X_5$  are selected from the group consisting of phenylalanine and tyrosine,  $X_3$  is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and  $X_4$  is selected from group consisting of tryptophan, tyrosine and phenylalanine.  
5
29. The amino acid sequence according to claim 28 wherein  $X_3$  is selected from the group consisting of aspartic acid and glutamic acid.
- 10 30. The amino acid sequence according to claim 29 wherein  $X_1$  and  $X_5$  are phenylalanine and  $X_2$  is tyrosine.
31. The amino acid sequence according to claim 29 wherein  $X_4$  is tryptophan.
32. The amino acid sequence according to claim 31 wherein  $X_3$  is aspartic acid to result in an amino acid sequence comprising FYDWF.
- 15 33. The amino acid sequence according to claim 31 wherein  $X_3$  is glutamic acid to result in an amino acid sequence comprising FYEWF.
34. The amino acid sequence according to claim 28 wherein the amino acid sequence FHEN is bound to the amino terminal of  $X_1X_2X_3X_4X_5$  to produce an amino acid sequence comprising FHEN $X_1X_2X_3X_4X_5$ .
- 20 35. The amino acid sequence according to claim 34 wherein the amino acid sequence comprises FHENFYDWF.

36. The amino acid sequence according to claim 25 wherein the amino acid sequence  $X_1X_2X_3X_4X_5$  further comprises the amino acid sequence  $X_{93}X_{94}X_{95}X_{96}X_{97}$  located at the carboxy terminal end adjacent to  $X_5$  to form  $X_1X_2X_3X_4X_5X_{93}X_{94}X_{95}X_{96}X_{97}$ , wherein  $X_{93}$ ,  $X_{94}$  and  $X_{97}$  may be any amino acid,  $X_{95}$  is selected from the group consisting of glutamine, glutamic acid, alanine and lysine, and  $X_{96}$  is a hydrophobic or aliphatic amino acid.

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37. The amino acid sequence according to claim 36 wherein  $X_{93}$  is selected from the group consisting of alanine, aspartic acid, glutamic acid, arginine, and valine,  $X_{95}$  is glutamine or glutamic acid, and  $X_{96}$  is selected from the group consisting of leucine, isoleucine, valine and tryptophan.

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38. The amino acid sequence according to claim 37 wherein  $X_{96}$  is leucine or tryptophan.

39. The amino acid sequence according to claim 38 wherein  $X_{96}$  is leucine.

40. The amino acid sequence according to claim 39 wherein  $X_{95}$  is glutamine, and  $X_{96}$  is tryptophan.

15

41. The amino acid sequence according to claim 40 wherein  $X_{93}$  is valine.

42. The amino acid sequence according to claim 41 wherein asparagine is bound to the amino terminal of  $X_1$ .

43. An amino acid sequence selected from the amino acid sequences listed in Figures 1-A through 1-O.

20

44. The amino acid sequence according to claim 25 wherein the sequence is selected from the group consisting of FHENFYDWFVRQVS, DYKDVTFTSAVFHENFYDWFVRQVSKK, GRVDWLQRNANFYDWFVAELG and APTFYAWFNQQT.

5 45. The amino acid sequence according to claim 25 wherein the sequence comprises FHENFYDWFVRQVS.

46. The amino acid sequence according to claim 25 wherein the sequence is selected from the group consisting of

10 FHENFYDWFVRQVAKK-NH<sub>2</sub>  
FHENFYDWFVRQASKK-NH<sub>2</sub>  
FHENFYDWFVRAVSKK-NH<sub>2</sub>  
FHENFYDWFVAQVSKK-NH<sub>2</sub>  
FHENFYDWFARQVSKK-NH<sub>2</sub>  
15 FHEAFYDWFVRQVSKK-NH<sub>2</sub>  
FHANFYDWFVRQVSKK-NH<sub>2</sub>  
FAENFYDWFVRQVSKK-NH<sub>2</sub>  
AHENFYDWFVRQVSKK-NH<sub>2</sub>  
fhenydwfvrvskk  
EFHENFYDWFVRQVSEE  
20 FHENFYGWFVRQVSKK  
HETFYSMIRSLAK  
SDGFYNAIELLS  
SLNFYDALQLLAKK  
•HDPFYSMMSLLK  
25 NSFYEALRMLSSK  
HPTSKIEIYAKLLK  
HPSTNQMLMKLFK  
HPPLSELKLFLIKK  
HAPLSVLVQALLKK  
30 HPSLSDMRWILLK  
WSDFYSYFQGLD  
D117-Dap(D117)  
SSNFYQALMLLS  
D117-Dap(CO-CH<sub>2</sub>-O-NH<sub>2</sub>)  
35 HENFYGWFVRQVSKK  
D117-Lys(D117)

	D117-b-Ala-Lys(D117)
	D117-b-Ala-Dap(b-Ala-D117)
	D117-Gly-Lys(Gly-D117)
5	D117-b-Ala-Lys(b-Ala-D117)
	D117-Dab(D117)
	D117-Orn(D117)
	D117-Dap(b-Ala-D117)
10	D117-b-Ala-Orn(b-Ala-D117)
	<u>1</u> -(Thia-b-Ala-D117) <sub>2</sub>
	FHENFYDWFVRQVS
	FHENFYDWFVRQVSK
	FHENFYDWFVQVSK
15	FHENFYDWFVVSK
	FHENFYDWFVSK
	FYDWF-NH <sub>2</sub>
	FYDWFKK-NH <sub>2</sub>
	AFYDWFAKK-NH <sub>2</sub>
20	AAAAFYDWFAAAAACKK-NH <sub>2</sub>
	(D117) <sub>2</sub> -12
	(Cys-Gly-D117) <sub>2</sub>
	Cys-Gly-D117
	(D117) <sub>2</sub> -14
25	LDALDRMLRYFEERPSL-NH <sub>2</sub>
	PLAELWAYFEHSEQGRSSAH-NH <sub>2</sub>
	GRVDWLQRNANFYDWFVAELG-NH <sub>2</sub>
	NGVERAGTGDNFYDWFVAQLH-NH <sub>2</sub>
	EHWNTVDPFYFTLFEWLRESG-NH <sub>2</sub>
30	EHWNTVDPFYQYFSELLRESG-NH <sub>2</sub>
	QSDSGTVHDRFYGWFRDTWAS-NH <sub>2</sub>
	AFYDWFAK-NH <sub>2</sub>
	AFYDWFA-NH <sub>2</sub>
	AFYDWF-NH <sub>2</sub>
35	FYDWDA-NH <sub>2</sub>
	Ac-FYDWF-NH <sub>2</sub>
	Lig-FHENFYDWFVRQVSKK
	Lig-GGGFHENFYDWFVRQVSKK
	FHENFYDWFVRQVSKKG-GG-Lig
	Lig-CAWPTYWNCG
40	ACAWPTYWNCG-Lig
	ACAWPTYWNCGGGG-Lig
	Lig-SDGFYNAIELLS
	SDGFYNAIELLS-Lig

SDGFYNAIELLSGGG-Lig  
KHLCVLEELFWGASLFGYCSGKK-Lig  
AFYDWFAKK-Lig  
AFYEWFAKK-NH<sub>2</sub>  
5 AFYGWFAKK-NH<sub>2</sub>  
AFYKWFAKK-NH<sub>2</sub>  
(SDGFYNAIELLS-Lig)<sub>2</sub>-14  
(AFYDWFAKK-Lig)<sub>2</sub>-14  
10 FHENAYDWFVRQVSKK  
FHENFADWFVRQVSKK  
FHENFYAWFVRQVSKK  
FHENFYDAFVRQVSKK  
FHENFTDWA VRQVSKK  
FQSLLEELVWGAPLFRYGTG  
15 PLCVLEELFWGASLFGQCSG  
QLEEEWAGVQCEVYGRECPS  
Cys-(Gly)<sub>2</sub>-D117  
(Cys-(Gly)<sub>2</sub>-D117)<sub>2</sub>  
(S210)-14-(S212)  
20 (S131)-14-(S212)  
(S205)<sub>2</sub>-14  
(S204)<sub>2</sub>-14  
(S131)-14-(S210)  
RVDWLQRNANFYDWFVAELG  
25 VDWLQRNANFYDWFVAELG  
DWLQRNANFYDWFVAELG  
WLQRNANFYDWFVAELG  
LQRNANFYDWFVAELG  
QRNANFYDWFVAELG  
30 RNANFYDWFVAELG  
NANFYDWFVAELG  
ANFYDWFVAELG  
NFYDWFVAELG  
GRVDWLQRNANFYDWFVAELG-Lig  
35 Lig-GRVDWLQRNANFYDWFVAELG  
(S208)-14-(S131)  
(S208)-14-(S209)  
GRVDWLQRNANFYDWFVAEL  
GRVDWLQRNANFYDWFVAE  
40 GRVDWLQRNANFYDWFVA  
GRVDWLQRNANFYDWFV  
14-(SDGFYNAIELLS-Lig)<sub>2</sub>  
(GRVDWLQRNANFYDWFVAELG)-14

14-(GRVDWLQRNANFYDWFVAE LG)  
(SDGFYNAIELLSGGG)<sub>2</sub>-14  
H-Acy-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub>  
5 RWPNFYGYFESLLTHFS-NH<sub>2</sub>  
HYNAFYEYFQVLLAETW-NH<sub>2</sub>  
EGWDFYSYFSGLLASVT-NH<sub>2</sub>  
LDRQFYRYFQDLLVGFM-NH<sub>2</sub>  
WGRSFYRYFETLLAQGI-NH<sub>2</sub>  
PLCFLQELFGGASLGGYCSG-NH<sub>2</sub>  
10 WLEQERAWIWCEIQGSGCRA-NH<sub>2</sub>  
IQGWEPFYGWFDDVVAQMFEET-NH<sub>2</sub>  
TGHRLGLDEQFYWWFRDALSG-NH<sub>2</sub>  
H-Abu-CLEE-w-GASL-Tic-QCSG-NH<sub>2</sub>  
15 14-(Dap-CAWPTYWNCG)<sub>2</sub>  
RDHypFYDWFDDi-NH<sub>2</sub>  
S131-14-S209  
S294-14-S210  
S295-14-S210  
S294-14-204  
20 S295-14-S204  
GFREGQRWYWFVAQVT-NH<sub>2</sub>  
VASGHVLHGQFYRWFVDQFALEE-NH<sub>2</sub>  
VGDFCVSHDCFYGWFLRESMQ-NH<sub>2</sub>  
DLRVLCELFGGAYVLGYCSE-NH<sub>2</sub>  
25 HLSVGEELSWWVALLGQWAR-NH<sub>2</sub>  
APVSTEELRWGALLFGQWAG-NH<sub>2</sub>  
ALEEEWA WVQVRSIRSGLPL-NH<sub>2</sub>  
WLEHEWAQIQCELYGRGCTY-NH<sub>2</sub>  
AAVHEQFYDWFADQYEE-NH<sub>2</sub>  
30 QAPSNFYDWFVREWDEE-NH<sub>2</sub>  
QSFYDYIEELLGGEWKK-NH<sub>2</sub>  
DPFYQGLWEWLRESGEE-NH<sub>2</sub>  
(S204)<sub>2</sub>-7  
(S204)<sub>2</sub>-9  
35 (S204)<sub>2</sub>-12  
(S204)<sub>2</sub>-13  
DWLQRNANFYDWFVAEL-Lig  
Lig-DWLQRNANFYDWFVAEL  
(S209)<sub>2</sub>-9  
40 (S210)<sub>2</sub>-9  
LigKHLCVLEELFWGASLFGYCSGKKKK  
KHLCVLEELFWGASLFGYCSGKKKK-Lig  
(S294)<sub>2</sub>-14

(S295)<sub>2</sub>14

S-D-G-F-Y-N-A-Acy-E-L-L-S

S-G-P-F-Y-E-E-Acy-E-L-L-W-Aib

G-G-S-F-Y-D-D-Acy-E-Aib-L-W-Aib

5 N-Aib-P-F-Y-D-E-Acy-D-E-Cha-W-Aib

GRVDWLQRNANFYDWFVAEAcG-NH<sub>2</sub>

and wherein underlined numbers represent a linker as defined in Table 18.

47. An amino acid sequence which specifically binds IR such that binding to IGF-1R is at or below background and wherein said amino acid sequence comprises X<sub>1</sub>X<sub>2</sub>X<sub>3</sub>X<sub>4</sub>X<sub>5</sub> wherein X<sub>1</sub>, X<sub>2</sub>, and X<sub>5</sub> are selected from the group consisting of phenylalanine and tyrosine, X<sub>3</sub> is selected from the group consisting of aspartic acid, glutamic acid, glycine and serine, and X<sub>4</sub> is selected from group consisting of tryptophan, tyrosine and phenylalanine.

10 48. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the sequence of amino acids X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>X<sub>11</sub>X<sub>12</sub>X<sub>13</sub> wherein X<sub>6</sub> and X<sub>7</sub> are aromatic amino acids or glutamine, X<sub>8</sub>, X<sub>9</sub>, X<sub>11</sub> and X<sub>12</sub> may be any amino acid, X<sub>10</sub> and X<sub>13</sub> are hydrophobic amino acids.

15 49. The method according to claim 48 wherein X<sub>6</sub> and X<sub>7</sub> are selected from group consisting of phenylalanine and tyrosine, and X<sub>10</sub> and X<sub>13</sub> are selected from group consisting of leucine, isoleucine, tryptophan, phenylalanine methionine and valine.

20 50. The method according to claim 48 wherein X<sub>6</sub> is phenylalanine and X<sub>7</sub> is tyrosine.

25 51. The method according to claim 50 wherein X<sub>10</sub> is isoleucine.

52. The method according to claim 50 wherein X<sub>10</sub> is leucine.

53. The method according to claim 50 wherein  $X_{13}$  is leucine.

54. The method according to claim 50 wherein  $X_9$  is tyrosine and  $X_{10}$  is phenylalanine.

55. The method according to claim 50 wherein the amino acid sequence is selected from  $FYX_8X_9LX_{11}X_{12}L$ ,  $FYX_8X_9IX_{11}X_{12}L$  and  $FYX_8YFX_{11}X_{12}L$ .

56. The method according to claim 55 wherein the amino acid sequence comprises  $FYX_8X_9LX_{11}X_{12}L$ .

57. The method according to claim 55 wherein the amino acid sequence comprises  $FYX_8YFX_{11}X_{12}L$ .

10 58. The method according to claim 48 wherein the amino acid sequence  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  further comprises amino acids  $X_{98}$  and  $X_{99}$  at the amino terminal end and  $X_{100}$  at the carboxy terminal end to form  $X_{98}X_{99}X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{100}$  and wherein  $X_{98}$  is optionally aspartic acid and  $X_{99}$  is independently an amino acid selected from the group consisting of glycine, glutamine and proline, and  $X_{100}$  is a hydrophobic amino acid.

15 59. The method according to claim 58 wherein  $X_{100}$  is an aliphatic amino acid.

60. The method according to claim 59 wherein  $X_{100}$  is leucine.

20 61. The method according to claim 48 wherein the amino acid sequence binds to the insulin receptor with an affinity of at least about  $10^{-5}$  M.

62. The method according to claim 61 wherein the affinity is between about  $10^{-7}$  M.

63. The method according to claim 48 wherein the amino acid sequence comprises DYKDFYDAIDQLVRGSARAGGTRD or

5 KDRAFYNGLRDLVGA VYGA WD.

64. The method according to claim 48 wherein the amino acid sequence is selected from the group of amino acid sequences listed in Figures 2A through 2P.

65. An amino acid sequence comprising  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids and wherein said amino acid sequence binds to IGF-1R.

10 66. The amino acid sequence according to claim 65 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.

15 67. The amino acid sequence according to claim 66 wherein the binding occurs at an affinity ( $K_d$ ) of at least about  $10^{-7}$  M.

68. The amino acid sequence according to claim 65 wherein  $X_6$  and  $X_7$  are phenylalanine or tyrosine, and  $X_{10}$  and  $X_{13}$  are leucine, isoleucine, tryptophan, phenylalanine or methionine.

20 69. The amino acid sequence according to claim 68 wherein  $X_6$  is phenylalanine and  $X_7$  is tyrosine.

70. The amino acid sequence according to claim 68 wherein  $X_{10}$  is isoleucine.
71. The amino acid sequence according to claim 68 wherein  $X_{10}$  is leucine.
72. The amino acid sequence according to claim 69 wherein  $X_{13}$  is leucine.
73. The amino acid sequence according to claim 69 wherein  $X_9$  is tyrosine and  
5  $X_{10}$  is phenylalanine.
74. The amino acid sequence according to claim 68 wherein the amino acid  
sequence comprises an amino acid sequence selected from  
 $FYX_8X_9LX_{11}X_{12}L$ ,  $FYX_8X_9IX_{11}X_{12}L$  and  $FYX_8YFX_{11}X_{12}L$ .
75. The amino acid sequence according to claim 74 wherein the amino acid  
sequence comprises  $FYX_8X_9IX_{11}X_{12}L$ .  
10
76. The amino acid sequence according to claim 74 wherein the amino acid  
sequence comprises  $FYX_8X_9LX_{11}X_{12}L$ .
77. The amino acid sequence according to claim 74 wherein the amino acid  
sequence is  $FYX_8YFX_{11}X_{12}L$ .
- 15 78. The amino acid sequence according to claim 65 wherein the amino acid  
sequence  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  further comprises amino acids  $X_{98}$  and  
 $X_{99}$  at the amino terminal end and  $X_{100}$  at the carboxy terminal end to form  
 $X_{98}X_{99}X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{100}$  and wherein  $X_{98}$  is optionally aspartic  
20 acid and  $X_{99}$  is independently an amino acid selected from the group  
consisting of glycine, glutamine and proline, and  $X_{100}$  is a hydrophobic  
amino acid.

79. The amino acid sequence according to claim 78 wherein  $X_{100}$  is an aliphatic amino acid.

80. The amino acid sequence according to claim 79 wherein  $X_{100}$  is leucine.

5 81. The amino acid sequence according to claim 68 wherein the amino acid sequence comprises DYKDFYDAIDQLVRGSARAGGTRD or KDRAFYNGLRDLVGA VYGA WDKK.

82. The sequence according to claim 81 wherein the amino acid sequence comprises DYKDFYDAIDQLVRGSARAGGTRD.

10 83. An amino acid sequence comprising an amino acid sequence selected from the group consisting of amino sequences listed in Figures 2A through 2P.

84. An amino acid sequence comprising a sequence selected from the group consisting of

15 SFYEAIHQLLGV,  
NSFYEALRMLSS,  
SLNFYDALQLLA,  
SSNFYQALMLLS,  
SDGFYNAIELLS,  
HETFYSMIRSLA,  
20 HDPFYSMMKSLL and  
WSDFYSYFQGLD.

85. The amino acid sequence according to claim 65 wherein the sequence comprises the amino acid sequence  
X<sub>115</sub>X<sub>116</sub>X<sub>117</sub>X<sub>118</sub>FYX<sub>8</sub>YFX<sub>11</sub>X<sub>12</sub>LX<sub>119</sub>X<sub>120</sub>X<sub>121</sub>X<sub>122</sub> wherein X<sub>115</sub> is selected from the group consisting of tryptophan, glycine, aspartic acid, glutamic acid and arginine, X<sub>116</sub> is selected from the group consisting of aspartic acid, histidine, glycine and asparagine, X<sub>117</sub> and X<sub>118</sub> are selected from the group consisting of glycine, aspartic acid, glutamic acid, asparagine, and alanine, X<sub>8</sub> is selected from the group consisting of arginine, glycine, glutamic acid and serine, X<sub>11</sub> is selected from the group consisting of glutamic acid, asparagine, glutamine and tryptophan, X<sub>12</sub> is selected from the group consisting of aspartic acid, glutamic acid, glycine, lysine, and glutamine, X<sub>119</sub> is selected from the group consisting of glutamic acid, glycine, glutamine, aspartic acid and alanine, X<sub>120</sub> is selected from the group consisting of glutamic acid, aspartic acid, glycine and glutamine, X<sub>121</sub> is selected from the group consisting of tryptophan, tyrosine, glutamic acid, phenylalanine, histidine and aspartic acid, and X<sub>122</sub> is selected from the group consisting of glutamic acid, aspartic acid, and glycine.

86. The amino acid sequence according to claim 85 wherein X<sub>115</sub> is tryptophan, X<sub>117</sub> is selected from glycine, aspartic acid, glutamic acid and asparagine; X<sub>118</sub> is selected from glycine, aspartic acid, glutamic acid and alanine; X<sub>11</sub>, X<sub>119</sub>, X<sub>120</sub>, and X<sub>122</sub> are glutamic acid; X<sub>12</sub> is aspartic acid, and X<sub>121</sub> is tryptophan or tyrosine.

87. An amino acid sequence comprising X<sub>6</sub>X<sub>7</sub>X<sub>8</sub>X<sub>9</sub>X<sub>10</sub>X<sub>11</sub>X<sub>12</sub>X<sub>13</sub> wherein X<sub>6</sub> and X<sub>7</sub> are aromatic amino acids or glutamine, X<sub>8</sub>, X<sub>9</sub>, X<sub>11</sub> and X<sub>12</sub> may be any amino acid, X<sub>10</sub> and X<sub>13</sub> are hydrophobic amino acids and wherein said amino acid sequence binds to IR such that binding to IGF-1R is at or below background.

88. A method of binding to Site 1 of IR from mammalian cells, said method comprising contacting IR with an amino acid sequence which binds IR and comprises the sequence of  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

5

89. The method according to claim 88 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.

10 90. The method according to claim 89 wherein  $X_{14}$  and  $X_{17}$  are leucine.

91. The method according to claim 89 wherein  $X_{14}$  is leucine.

92. The method according to claim 89 wherein  $X_{17}$  is leucine.

93. The method according to claim 89 wherein  $X_{20}$  is tyrosine.

94. The method according to claim 89 wherein  $X_{21}$  is phenylalanine.

15 95. The method according to claim 90 wherein  $X_{15}$  is a large amino acid.

96. The method according to claim 89 wherein said amino acid sequence further comprises an amino acid extension comprising  $X_{101}X_{102}X_{103}$  wherein  $X_{103}$  is bound to  $X_{14}$  at the amino terminus and  $X_{101}$  and  $X_{102}$  are polar amino acids and  $X_{103}$  is a hydrophobic amino acid.

20 97. The method according to claim 96 wherein  $X_{101}$  and  $X_{102}$  are independently aspartic acid or glutamic acid and  $X_{103}$  is leucine, isoleucine or valine.

98. A method of binding to Site 1 of IGF-1R from mammalian cells, said method comprising contacting IGF-1R with an amino acid sequence which binds IR and comprises the sequence of  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

5

99. The method according to claim 98 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{18}$  is an aromatic amino acid;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.

10 100. The method according to claim 98 wherein the amino acid sequence comprises a sequence selected from the sequences in Figures 3A through 3D.

101. An amino acid sequence which binds Site 1 of IR from mammalian cells, said sequence comprising  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

15

102. The amino acid sequence according to claim 101 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{20}$  is selected from group consisting of phenylalanine and tyrosine.

20 103. The amino acid sequence according to claim 102 wherein  $X_{14}$  and  $X_{17}$  are leucine.

104. The amino acid sequence according to claim 102 wherein  $X_{14}$  is leucine.

105. The amino acid sequence according to claim 102 wherein  $X_{17}$  is leucine.

106. The amino acid sequence according to claim 102 wherein amino acid  $X_{18}$  is tryptophan.

107. The amino acid sequence according to claim 103 wherein  $X_{20}$  is tyrosine.

108. The amino acid sequence according to claim 107 wherein  $X_{21}$  is phenylalanine.

109. The amino acid sequence according to claim 103 wherein  $X_{15}$  is a large amino acid.

110. The amino acid sequence according to claim 101 wherein at least one amino acid is a D-amino acid.

10 111. The amino acid sequence according to claim 65 wherein at least one amino acid is a D-amino acid.

112. The amino acid sequence according to claim 102 wherein said amino acid sequence further comprises an amino acid extension comprising  $X_{101}X_{102}X_{103}$  wherein  $X_{103}$  is bound to  $X_{14}$  at the amino terminus and  $X_{101}$  and  $X_{102}$  are polar amino acids and  $X_{103}$  is a hydrophobic amino acid.

15 113. The amino acid sequence according to claim 112 wherein  $X_{101}$  and  $X_{102}$  are independently aspartic acid or glutamic acid and  $X_{103}$  is leucine, isoleucine or valine.

114. An amino acid sequence which binds Site 1 of IGF-1R from mammalian cells such that binding to IR is at or below background, said sequence comprising  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

5

115. The amino acid sequence according to claim 114 wherein  $X_{14}$  and  $X_{17}$  are selected from the group consisting of leucine, isoleucine and valine;  $X_{18}$  is an aromatic amino acid;  $X_{20}$  is selected from group consisting of tyrosine and histidine; and  $X_{21}$  is selected from group consisting of phenylalanine and tyrosine.

10

116. A method of binding to Site 2 of IR from mammalian cells, said method comprising contacting said cells with an amino acid sequence comprising  $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$  wherein  $X_{22}$ ,  $X_{25}$ ,  $X_{26}$ ,  $X_{28}$ ,  $X_{29}$ ,  $X_{30}$ ,  $X_{31}$ ,  $X_{33}$ ,  $X_{34}$ ,  $X_{35}$ ,  $X_{37}$ ,  $X_{38}$ ,  $X_{39}$ ,  $X_{40}$  and  $X_{41}$  are any amino acid;  $X_{23}$  is any hydrophobic amino acid;  $X_{27}$  is a polar amino acid;  $X_{31}$  is an aromatic amino acid;  $X_{32}$  is a small amino acid; and wherein at least one cysteine is located at positions  $X_{24}$  through  $X_{27}$  and one at  $X_{39}$  or  $X_{40}$ .

15

117. The method according to claim 116 wherein  $X_{24}$  and  $X_{39}$  are cysteines.

20

118. The method according to claim 117 wherein  $X_{23}$  is selected from leucine, isoleucine, methionine and valine;  $X_{27}$  is selected from glutamic acid, aspartic acid, asparagine, and glutamine;  $X_{31}$  is tryptophan,  $X_{32}$  is glycine; and  $X_{36}$  is any aromatic amino acid.

25

119. The method according to claim 118 wherein the binding to IR occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.

120. The method according to claim 116 wherein  $X_{23}$  is leucine,  $X_{27}$  is glutamic acid,  $X_{31}$  is tryptophan, and  $X_{32}$  is glycine.

121. The method according to claim 116 wherein the amino acid sequence is HLCVLEELFWGASLFGYCSG.

5 122. An amino acid sequence which binds IR, said amino acid sequence comprising  
 $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}$   
wherein  $X_{22}$ ,  $X_{25}$ ,  $X_{26}$ ,  $X_{28}$ ,  $X_{29}$ ,  $X_{30}$ ,  $X_{33}$ ,  $X_{34}$ ,  $X_{35}$ ,  $X_{36}$ ,  $X_{37}$ ,  $X_{38}$ ,  $X_{40}$  and  $X_{41}$  are any amino acid,  $X_{23}$  is any hydrophobic amino acid,  $X_{27}$  is a polar amino acid;  $X_{31}$  is an aromatic amino acid;  $X_{32}$  is a small amino acid, and wherein at least one cysteine is located at positions  $X_{24}$  through  $X_{27}$  and one at  $X_{39}$  or  $X_{40}$ .

123. The amino acid sequence according to claim 122 wherein  $X_{24}$  and  $X_{39}$  are cysteines.

15 124. The amino acid sequence according to claim 123 wherein  $X_{23}$  is selected from methionine, valine, and leucine;  $X_{27}$  is selected from glutamic acid, alanine, glycine, glutamine, aspartic acid and valine;  $X_{31}$  and  $X_{32}$  are small amino acids; and  $X_{36}$  is an aromatic amino acid.

20 125. The amino acid sequence according to claim 122 wherein the binding to IR occurs at an affinity ( $K_d$ ) of at least about  $10^{-5}$  M.

126. The amino acid sequence according to claim 124 wherein  $X_{23}$  is leucine,  $X_{27}$  is glutamic acid,  $X_{31}$  is tryptophan, and  $X_{32}$  is glycine.

127. The amino acid sequence according to claim 122 wherein the amino acid sequence is HLCVLEELFWGASLFGYCSG.

128. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises the sequence X<sub>42</sub> X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> X<sub>46</sub> X<sub>47</sub> X<sub>48</sub> X<sub>49</sub> X<sub>50</sub> X<sub>51</sub> X<sub>52</sub> X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub> X<sub>57</sub> X<sub>58</sub> X<sub>59</sub> X<sub>60</sub> X<sub>61</sub> wherein X<sub>42</sub>, X<sub>43</sub>, X<sub>44</sub>, X<sub>45</sub>, X<sub>53</sub>, X<sub>55</sub>, X<sub>56</sub>, X<sub>58</sub>, X<sub>60</sub> and X<sub>61</sub> are any amino acid; X<sub>43</sub>, X<sub>46</sub>, X<sub>49</sub>, X<sub>50</sub> and X<sub>54</sub> are hydrophobic amino acids; X<sub>47</sub> and X<sub>59</sub> are cysteines; X<sub>48</sub> is a polar amino acid; X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are small amino acids.

129. The method according to claim 128 wherein X<sub>43</sub> and X<sub>46</sub> are leucine; X<sub>48</sub> is selected from the group consisting of aspartic acid and glutamic acid; X<sub>50</sub> is phenylalanine or tyrosine; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are glycine.

130. The method according to claim 129 wherein X<sub>48</sub> is glutamic acid and X<sub>50</sub> is a phenylalanine.

131. The method according to claim 130 wherein the amino acid sequence is X<sub>42</sub> X<sub>43</sub> X<sub>44</sub> X<sub>45</sub>LCE X<sub>49</sub> FGG X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub>GX<sub>58</sub>C X<sub>60</sub> X<sub>61</sub>.

132. The method according to claim 131 wherein the amino acid sequence comprises DLRVLCELFGGAYVLGYCSE or DLRVLCELFGGAYVRGYCSE.

133. The method according to claim 128 wherein the binding to IR occurs at an affinity (K<sub>d</sub>) of at least about 10<sup>-5</sup> M.

134. An amino acid sequence which binds IR, said amino acid sequence comprising X<sub>42</sub> X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> X<sub>46</sub> X<sub>47</sub> X<sub>48</sub> X<sub>49</sub> X<sub>50</sub> X<sub>51</sub> X<sub>52</sub> X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub> X<sub>57</sub> X<sub>58</sub> X<sub>59</sub> X<sub>60</sub> X<sub>61</sub> wherein X<sub>42</sub>, X<sub>43</sub>, X<sub>44</sub>, X<sub>45</sub>, X<sub>53</sub>, X<sub>55</sub>, X<sub>60</sub> and X<sub>61</sub> are any amino acid; X<sub>43</sub>, X<sub>46</sub>, X<sub>49</sub>, X<sub>50</sub> and X<sub>54</sub> are hydrophobic amino acids; X<sub>47</sub> and X<sub>59</sub> are cysteines; X<sub>48</sub> is a polar amino acid; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are small amino acids.

5

135. The amino acid sequence according to claim 134 wherein X<sub>43</sub> and X<sub>46</sub> are leucine; X<sub>48</sub> is selected from the group consisting of aspartic acid and glutamic acid; X<sub>50</sub> is phenylalanine or tyrosine; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are glycine.

10

136. The amino acid sequence according to claim 135 wherein X<sub>48</sub> is glutamic acid and X<sub>50</sub> is phenylalanine.

137. The amino acid sequence according to claim 136 wherein the amino acid sequence comprises X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> LCE X<sub>49</sub> FGG X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> X<sub>56</sub> G X<sub>58</sub> C X<sub>60</sub> X<sub>61</sub>.

15

138. The amino acid sequence according to claim 137 wherein an amino acid sequence comprises DLRVLCELFGGAYVLGYCSE or DLRVLCELFGGAYVRGYCSE

139. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising X<sub>62</sub> X<sub>63</sub> X<sub>64</sub> X<sub>65</sub> X<sub>66</sub> X<sub>67</sub> X<sub>68</sub> X<sub>69</sub> X<sub>70</sub> X<sub>71</sub> X<sub>72</sub> X<sub>73</sub> X<sub>74</sub> X<sub>75</sub> X<sub>76</sub> X<sub>77</sub> X<sub>78</sub> X<sub>79</sub> X<sub>80</sub> X<sub>81</sub> wherein X<sub>62</sub>, X<sub>65</sub>, X<sub>66</sub> X<sub>68</sub>, X<sub>69</sub>, X<sub>71</sub>, X<sub>73</sub>, X<sub>76</sub>, X<sub>77</sub>, X<sub>78</sub>, X<sub>80</sub> and X<sub>81</sub> are any amino acid; X<sub>63</sub>, X<sub>70</sub>, and X<sub>74</sub> are hydrophobic amino acids; X<sub>64</sub> is a polar amino acid; X<sub>67</sub> and X<sub>75</sub> are aromatic amino acids; and X<sub>72</sub> and X<sub>79</sub> are cysteines.

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140. The method according to claim 139 wherein  $X_{63}$  is selected from the group consisting of leucine, isoleucine, methionine and valine;  $X_{70}$  and  $X_{74}$  are selected from group consisting of valine, isoleucine, leucine and methionine;  $X_{64}$  is selected from group consisting of aspartic acid and glutamic acid;  $X_{67}$  is tryptophan; and  $X_{75}$  is selected from group consisting of tyrosine and tryptophan.

5

141. The method according to claim 140 wherein  $X_{66}$  is glutamic acid.

142. The method according to claim 141 wherein  $X_{63}$  is leucine.

143. The method according to claim 140 wherein  $X_{74}$  is valine.

10 144. The method according to claim 141 wherein  $X_{64}$  is a glutamic acid.

145. The method according to claim 141 wherein  $X_{75}$  is a tyrosine.

146. The method accord to claim 140 wherein the amino acid sequence comprises WLDQEWA WVQCEVYGRGCPS.

15 147. An amino acid sequence which binds IR, said amino acid sequence comprising  $X_{62}$   $X_{63}$   $X_{64}$   $X_{65}$   $X_{66}$   $X_{67}$   $X_{68}$   $X_{69}$   $X_{70}$   $X_{71}$   $X_{72}$   $X_{73}$   $X_{74}$   $X_{75}$   $X_{76}$   $X_{77}$   $X_{78}$   $X_{79}$   $X_{80}$   $X_{81}$  wherein  $X_{62}$ ,  $X_{65}$ ,  $X_{66}$   $X_{68}$ ,  $X_{69}$ ,  $X_{71}$ ,  $X_{73}$ ,  $X_{76}$ ,  $X_{77}$ ,  $X_{78}$ ,  $X_{80}$  and  $X_{81}$  are any amino acid;  $X_{63}$ ,  $X_{70}$ , and  $X_{74}$  are hydrophobic amino acids;  $X_{64}$  is a polar amino acid;  $X_{67}$  and  $X_{75}$  are aromatic amino acids; and  $X_{72}$  and  $X_{79}$  are cysteines.

148. The amino acid sequence according to claim 147 wherein  $X_{63}$  is selected from the group consisting of leucine, isoleucine, methionine and valine;  $X_{70}$  and  $X_{74}$  are selected from group consisting of valine, isoleucine, leucine and methionine;  $X_{64}$  is selected from group consisting of aspartic acid and glutamic acid;  $X_{67}$  is tryptophan; and  $X_{75}$  is selected from group consisting of tyrosine and tryptophan.

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149. The amino acid sequence according to claim 148 wherein  $X_{66}$  is glutamic acid.

150. The amino acid sequence according to claim 149 wherein  $X_{63}$  is leucine.

10 151. The amino acid sequence according to claim 148 wherein  $X_{74}$  is valine.

152. The amino acid sequence according to claim 149 wherein  $X_{64}$  is glutamic acid.

153. The amino acid sequence according to claim 148 wherein  $X_{75}$  is a tyrosine.

154. The amino acid sequence accord to claim 148 wherein the amino acid sequence comprises WLDQEWA WVQCEVYGRGCPS.

15

155. The amino acid sequence according to claim 148 wherein the affinity ( $K_d$ ) of binding to IR is at least  $10^{-5}$  M.

156. The amino acid sequence according to claim 148 wherein the amino acid sequence comprises a sequence selected from the sequences of Figures 6A-6F.

20

5 157. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence which binds IR and comprises  $HX_{82}X_{83}X_{84}X_{85}X_{86}X_{87}X_{88}X_{89}X_{90}X_{91}X_{92}$  herein  $X_{82}$  is proline or alanine;  $X_{83}$  is a small amino acid;  $X_{84}$  is selected from the group consisting of leucine, serine and threonine;  $X_{85}$  is a polar amino acid;  $X_{86}$  is any amino acid;  $X_{87}$  is an aliphatic amino acid;  $X_{88}$ ,  $X_{89}$ ,  $X_{90}$  is any amino acid; and  $X_{91}$  and  $X_{92}$  are aliphatic amino acids.

10 158. The method according to claim 157 wherein  $X_{82}$  is proline;  $X_{83}$  is selected from the group consisting of proline, serine and threonine;  $X_{84}$  is leucine;  $X_{85}$  is selected from the group consisting of glutamic acid, serine, lysine and asparagine;  $X_{86}$  is a polar amino acid;  $X_{87}$  is selected from the group consisting of leucine, methionine and isoleucine; and  $X_{91}$  and  $X_{92}$  are leucines.

15 159. The method according to claim 158 wherein  $X_{83}$  is proline.

160. The method according to claim 158 wherein  $X_{85}$  is serine.

161. The method according to claim 158 wherein  $X_{86}$  is selected from the group consisting of histidine, glutamic acid, aspartic acid and glutamine.

162. The method according to claim 158 wherein  $X_{87}$  is leucine.

163. The method according to claim 158 wherein  $X_{92}$  is phenylalanine.

20 164. The method according to claim 160 wherein the amino acid sequence is  $HPPLSX_{86} LX_{88} X_{89} X_{90} LL$ .

165. The method according to claim 158 wherein the amino acid sequence is selected from the group consisting of HPPLLEHLKAFLL, HPPLSELKLFLI, HPSLSDMRWILL, HPTSKEIYAKLL, HPTSKEIYAKLL, HPSTNQQLMKLF and HAPLSVLQALL.

5 166. An amino acid sequence which binds IR, said amino acid sequence comprising  $HX_{82}X_{83}X_{84}X_{85}X_{86}X_{87}X_{88}X_{89}X_{90}X_{91}X_{92}$  herein  $X_{82}$  is proline or alanine;  $X_{83}$  is a small amino acid;  $X_{84}$  is selected from the group consisting of leucine, serine and threonine;  $X_{85}$  is a polar amino acid;  $X_{86}$  is any amino acid;  $X_{87}$  is an aliphatic amino acid;  $X_{88}$ ,  $X_{89}$ ,  $X_{90}$  is any amino acid; and  $X_{91}$  and  $X_{92}$  are aliphatic amino acids.

10 167. The amino acid sequence according to claim 166 wherein  $X_{82}$  is proline;  $X_{83}$  is selected from the group consisting of proline, serine and threonine;  $X_{84}$  is leucine;  $X_{85}$  is selected from the group consisting of glutamic acid, serine, lysine and asparagine;  $X_{86}$  is a polar amino acid;  $X_{87}$  is selected from the group consisting of leucine, methionine and isoleucine; and  $X_{91}$  and  $X_{92}$  are leucines.

15 168. The amino acid sequence according to claim 167 wherein  $X_{83}$  is proline.

169. The amino acid sequence according to claim 167 wherein  $X_{85}$  is serine.

170. The amino acid sequence according to claim 167 wherein  $X_{86}$  is selected from the group consisting of histidine, glutamic acid, aspartic acid and glutamine.

20 171. The amino acid sequence according to claim 167 wherein  $X_{87}$  is leucine.

172. The amino acid sequence according to claim 167 wherein  $X_{92}$  is phenylalanine.
173. The amino acid sequence according to claim 169 wherein the amino acid sequence is HPPLSX<sub>86</sub> LX<sub>88</sub> X<sub>89</sub> X<sub>90</sub> LL.
- 5 174. The amino acid sequence according to claim 167 wherein the amino acid sequence is selected from the group consisting of HPPEHLKAFLL, HPPLSELKLFLI, HPSLSDMRWILL, HPTSKEIYAKLL, HPTSKEIYAKLL, HPSTNQMLMKLF and HAPLSVQLQALL.
- 10 175. A method modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising an amino acid sequence of  $X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}$  wherein at least one of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan; wherein  $X_{104}$  and  $X_{114}$  are both small amino acids; wherein  $X_{105}$  is any amino acid; and wherein at least one of  $X_{104}$ ,  $X_{105}$ ,  $X_{106}$  and one of  $X_{112}$   $X_{113}$   $X_{114}$  are cysteine residues.
- 15 176. The method according to claim 175 wherein at least two of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan which are separated from each other by at least two amino acids.
177. The method according to claim 176 wherein the separating amino acids are selected from the group consisting of proline, threonine and tyrosine.
- 20 178. The method according to claim 177 wherein the amino acid sequence comprises WPTYW.

179. The method according to claim 178 wherein  $X_{105}$  and  $X_{113}$  are cysteine residues.
180. The method according to claim 178 wherein  $X_{104}$  and  $X_{114}$  are selected from the group consisting of alanine and glycine.
- 5 181. The method according to claim 180 wherein  $X_{104}$  is alanine and  $X_{114}$  is glycine.
182. The method according to claim 181 wherein  $X_{105}$  is valine.
183. The method according to claim 182 wherein  $X_{112}$  is asparagine.
- 10 184. The method according to claim 198 wherein the affinity ( $K_d$ ) of binding to IR is at least about  $10^{-5}$  M.
185. A method of modulating insulin activity in mammalian cells, said method comprising administering to said cells an amino acid sequence comprising an amino acid sequence selected from the group listed in Figure 8.
- 15 186. The method according to claim 185 wherein the sequence comprises ACVWPTYWNCG.
187. An amino acid sequence which binds and IR and comprising an amino acid sequence of  $X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}$  wherein at least one of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan; wherein  $X_{104}$  and  $X_{114}$  are both small amino acids; wherein  $X_{105}$  is any amino acid; and wherein at least one of  $X_{104}$ ,  $X_{105}$ ,  $X_{106}$  and one of  $X_{112}$   $X_{113}$   $X_{114}$  are cysteine residues.

188. The amino acid sequence according to claim 187 wherein at least two of the amino acids of  $X_{106}$  through  $X_{111}$  are tryptophan which are separated from each other by at least two amino acids.

5 189. The amino acid sequence according to claim 188 wherein the separating amino acids are selected from the group consisting of proline, threonine and tyrosine.

190. The amino acid sequence according to claim 189 wherein the amino acid sequence comprises WPTYW.

10 191. The amino acid sequence according to claim 190 wherein  $X_{105}$  and  $X_{113}$  are cysteine residues.

192. The amino acid sequence according to claim 190 wherein  $X_{104}$  and  $X_{114}$  are selected from the group consisting of alanine and glycine.

193. The amino acid sequence according to claim 190 wherein  $X_{104}$  is alanine and  $X_{114}$  is glycine.

15 194. The amino acid sequence according to claim 193 wherein  $X_{105}$  is valine.

195. The amino acid sequence according to claim 194 wherein  $X_{112}$  is asparagine.

196. The amino acid sequence according to claim 202 wherein the affinity ( $K_d$ ) of binding to IR is at least about  $10^{-5}$  M.

20 197. An amino acid sequence which binds IR from mammalian cells comprising an amino acid sequence selected from the group listed in Figure 8.

198. The amino acid sequence according to claim 197 comprising  
ACVWPTYWNCG.

199. A method of providing insulin agonist activity to mammalian cells, said  
method comprising administering to said cells an amino acid sequence  
comprising DYKDLCQSWGVRIGWLAGLCPKK.

5 200. A method of modulating insulin activity in mammalian cells, said method  
comprising administering to said cells an amino acid sequence comprising  
an amino acid sequence selected from the group listed in Figures 9 through  
11.

10 201. An amino acid sequence comprising DYKDLCQSWGVRIGWLAGLCPKK.

202. An amino acid sequence comprising an amino acid sequence selected from  
the group listed in Figures 9 through 11.

15 203. An amino acid sequence comprising at least two amino acid sequences  
which independently bind IR, with the proviso that at least one of the  
sequences is not insulin or a fragment thereof.

204. The amino acid sequence according to claim 203 wherein the two amino  
acid sequences bind to Site 1 of IR.

205. The amino acid sequence according to claim 203 wherein one amino acid  
sequence binds to Site 1, and the other binds to Site 2 of IR.

206. The amino acid sequence according to claim 203, wherein at least one of the sequences is selected from the group consisting of  $X_1X_2X_3X_4X_5$  wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  may be any polar amino acid;  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids; and  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

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207. The amino acid sequence according to claim 206, wherein at least one of the sequences is  $X_1X_2X_3X_4X_5$  wherein  $X_1$ ,  $X_2$ ,  $X_4$ , and  $X_5$  are aromatic amino acids, and  $X_3$  may be any polar amino acid.

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208. The amino acid sequence according to claim 206 wherein at least one of the sequences comprises  $FYX_3WF$ .

209. The amino acid sequence according to claim 206, wherein at least one of the sequences comprises  $X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}$  wherein  $X_6$  and  $X_7$  are aromatic amino acids or glutamine,  $X_8$ ,  $X_9$ ,  $X_{11}$  and  $X_{12}$  may be any amino acid,  $X_{10}$  and  $X_{13}$  are hydrophobic amino acids.

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210. The amino acid sequence according to claim 209, wherein at least one of the sequences comprises  $FYX_8X_9LX_{11}X_{12}L$ .

20

211. The amino acid sequence according to claim 206, wherein at least one of the sequences comprises  $X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}$  wherein  $X_{14}$ ,  $X_{17}$ , and  $X_{18}$  are hydrophobic amino acids,  $X_{15}$ ,  $X_{16}$ , and  $X_{19}$  are any amino acid, and  $X_{20}$  and  $X_{21}$  are aromatic amino acids.

212. The amino acid sequence according to claim 211 wherein at least one of the sequences comprises LX<sub>15</sub>, X<sub>16</sub>, LLX<sub>19</sub>YF.

213. The amino acid sequence according to claim 203 wherein at least one of the sequences comprises

5 X<sub>22</sub>X<sub>23</sub>X<sub>24</sub>X<sub>25</sub>X<sub>26</sub>X<sub>27</sub>X<sub>28</sub>X<sub>29</sub>X<sub>30</sub>X<sub>31</sub>X<sub>32</sub>X<sub>33</sub>X<sub>34</sub>X<sub>35</sub>X<sub>36</sub>X<sub>37</sub>X<sub>38</sub>X<sub>39</sub>X<sub>40</sub>X<sub>41</sub> wherein X<sub>22</sub>, X<sub>25</sub>, X<sub>26</sub>, X<sub>28</sub>, X<sub>29</sub>, X<sub>30</sub>, X<sub>33</sub>, X<sub>34</sub>, X<sub>35</sub>, X<sub>36</sub>, X<sub>37</sub>, X<sub>38</sub>, X<sub>40</sub>, and X<sub>41</sub> are any amino acid, X<sub>23</sub> is any hydrophobic amino acid; X<sub>27</sub> is a polar amino acid; X<sub>31</sub> is an aromatic amino acid; X<sub>32</sub> is a small amino acid, and wherein at least one cysteine is located at positions X<sub>24</sub> through X<sub>27</sub> and one at X<sub>39</sub> or X<sub>40</sub>; X<sub>42</sub> X<sub>43</sub> X<sub>44</sub> X<sub>45</sub> X<sub>46</sub> X<sub>47</sub> X<sub>48</sub> X<sub>49</sub> X<sub>50</sub> X<sub>51</sub> X<sub>52</sub> X<sub>53</sub> X<sub>54</sub> X<sub>55</sub> 10 X<sub>56</sub>X<sub>57</sub>X<sub>58</sub>X<sub>59</sub> X<sub>60</sub> X<sub>61</sub> wherein X<sub>42</sub>, X<sub>43</sub>, X<sub>44</sub>, X<sub>45</sub>, X<sub>53</sub>, X<sub>55</sub>, X<sub>56</sub>, X<sub>58</sub>, X<sub>60</sub> and X<sub>61</sub> are any amino acid; X<sub>43</sub>, X<sub>46</sub>, X<sub>49</sub>, X<sub>50</sub> and X<sub>54</sub> are hydrophobic amino acids; X<sub>47</sub> and X<sub>59</sub> are cysteine; X<sub>48</sub> is a polar amino acid; and X<sub>51</sub>, X<sub>52</sub> and X<sub>57</sub> are small amino acids; or X<sub>62</sub> X<sub>63</sub> X<sub>64</sub> X<sub>65</sub> X<sub>66</sub> X<sub>67</sub> X<sub>68</sub> X<sub>69</sub> X<sub>70</sub> X<sub>71</sub> X<sub>72</sub> 15 X<sub>73</sub> X<sub>74</sub> X<sub>75</sub> X<sub>76</sub> X<sub>77</sub> X<sub>78</sub> X<sub>79</sub> X<sub>80</sub> X<sub>81</sub> wherein X<sub>62</sub>, X<sub>65</sub>, X<sub>66</sub> X<sub>68</sub>, X<sub>69</sub>, X<sub>71</sub>, X<sub>73</sub>, X<sub>76</sub>, X<sub>77</sub>, X<sub>78</sub>, X<sub>80</sub> and X<sub>81</sub> are any amino acid; X<sub>63</sub>, X<sub>70</sub>, and X<sub>74</sub> are hydrophobic amino acids; X<sub>64</sub> is a polar amino acid; X<sub>67</sub> and X<sub>75</sub> are aromatic amino acids; and X<sub>72</sub> and X<sub>79</sub> are cysteines.

214. The amino acid sequence according to claim 203 wherein at least one of the sequences comprises HX<sub>82</sub>X<sub>83</sub>X<sub>84</sub>X<sub>85</sub>X<sub>86</sub>X<sub>87</sub>X<sub>88</sub>X<sub>89</sub>X<sub>90</sub>X<sub>91</sub>X<sub>92</sub> herein X<sub>82</sub> is proline or alanine; X<sub>83</sub> is a small amino acid; X<sub>84</sub> is selected from the group consisting of leucine, serine and threonine; X<sub>85</sub> is a polar amino acid; X<sub>86</sub> is any amino acid; X<sub>87</sub> is an aliphatic amino acid; X<sub>88</sub>, X<sub>89</sub>, X<sub>90</sub> is any amino acid; and X<sub>91</sub> and X<sub>92</sub> are aliphatic amino acids or

20 X<sub>104</sub>X<sub>105</sub>X<sub>106</sub>X<sub>107</sub>X<sub>108</sub>X<sub>109</sub>X<sub>110</sub>X<sub>111</sub>X<sub>112</sub>X<sub>113</sub>X<sub>114</sub> wherein at least one of the amino acids of X<sub>106</sub> through X<sub>111</sub> are tryptophan; wherein X<sub>104</sub> and X<sub>114</sub> are both small amino acids; wherein X<sub>105</sub> is any amino acid; and wherein at least one of X<sub>104</sub>, X<sub>105</sub>, X<sub>106</sub> and one of X<sub>112</sub> X<sub>113</sub> X<sub>114</sub> are cysteine residues.

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215. The amino acid sequence according to claim 203 wherein the two amino acid sequences are connected by a peptide or non-peptide linker.
216. The amino acid sequence according to claim 215 wherein the linker is a peptide consisting of about 2 to about 16 amino acids.
- 5 217. The amino acid sequence according to claim 215 wherein the linker is a non-peptide.
218. The amino acid sequence according to claim 217 wherein the linker is dialdehyde.
- 10 219. The amino acid sequence according to claim 203 wherein the amino acid sequence is selected from the group consisting of

DYKDDDDKFHENFYDWFVRQVSGSGSGLDALDRLMRYGEERPSLA  
AAGAP,

DYKDDDDKFHENFYDWFVRQVSGGSHLCVLEELFWGASLFGYCSG  
AAAGAPVPYPDPLEPRAA,

15 DYKDDDDKFHENFYDWFVRQVSGGSGGSGGSHLCVLEELFWGASL  
FGYCSGAAAGAPVPYPDPLEPRAA,

DYKDDDDKFHENFYDWFVRQVSGGSGGSGGSHLCVLEELFWG  
ASLFGYCSGAAAGAPVPYPDPLEPRAA,

20 AQPAMAFHENFYDWFVRQVSGGSFHENFYDWFVRQVSAAAGAPVP  
YPDPLEPRAA,

AQPAMAFHENFYDWFVRQVSGGSFHENFYDWFVRQVSGGSFHENF  
YDWFVRQVSAAGAPVPYPDPLEPRAA,

AQPAMAFHENFYDWFVRQVSGGSGGSFHENFYDWFVRQVSAAG  
APVPYPDPLEPRAA,

5 AQPAMAFHENFYDWFVRQVSGGSGGSGGSFHENFYDWFVRQVSAA  
AGAPVPYPDPLEPRAA and

AQPAMAFHENFYDWFVRQVSGGSGGSGGSFHENFYDWFVRQV  
SAAAGAPVPYPDPLEPRAA.

220. A nucleic acid sequence encoding amino acid sequence which binds to IR at  
10 Site 1 and/or Site 2, with the proviso that the sequence is not insulin, IGF, or  
fragments thereof.

221. The nucleic acid sequence according to claim 220 wherein the nucleic acid  
sequence encodes for an amino acid sequence selected from the group  
consisting of FYDWF, FYEWF, FHENFYDWF, FHENFYDWFVRQVSK,  
15 DYKDVTFTSAVFHENFYDWFVRQVSKK, GRVDWLQRNANFYDWFV  
AELG and APTFYAWFNQQT.

222. The nucleic acid sequence according to claim 220 wherein the nucleic acid  
sequence encodes for an amino acid sequence selected from the group  
consisting of DYKDFYDAIDQLVRGSARAGGTRDKK and  
20 KDRAFYNGLRDLVGA VYGA WDKK.

223. The nucleic acid sequence according to claim 220 wherein the nucleic acid  
sequence encodes for an amino acid sequence selected from the group  
consisting of SFYEAIHQLLGV,

NSFYEARLMLSS,  
SLENFYDALQLLA,  
SSNFYQALMLLS,  
SDGFYNAIELLS,  
HETFYSMIRSLA,  
HDPFYSMMKSL and  
WSDFYSYFQGL.

10 224. A kit for identifying a compound which binds IGF-1 receptor, comprising IGF-1 receptor and an amino acid sequence selected from Formulas 1-10, or the amino acid sequences of Figures 9-11, which bind to the receptor at Site 1 or Site 2.

225. The kit according to claim 224, wherein the amino acid sequence comprises the amino acid sequence FYDWF.

15 226. The kit according to claim 225, wherein the amino acid sequence comprises the amino acid sequence SAKNFYDWVFVKK.

227. The kit according to claim 226 wherein the amino acid sequence comprises the amino acid sequence FYSLLASL.

228. The kit according to claim 227 wherein the amino acid sequence comprises the amino acid sequence QMKDIFYSLLASLAKK.

20 229. A kit for identifying a compound which binds IR comprising IR and an amino acid sequence selected from Formulas 1-10 or the amino acid sequences of Figures 9 and 11 which bind IR at Site 1 or Site 2.

220. A pharmaceutical composition comprising a amino acid sequence which binds specifically to IGF-1 receptor at Site 1 and is an IGF agonist, with the proviso that the amino acid sequence is not IGF-1, insulin, or fragments thereof, and a pharmaceutically acceptable carrier.

231. The composition according to claim 230, wherein the peptide comprises the amino acid sequence NFYDWVF.

232. The pharmaceutical composition according to claim 230, wherein the peptide comprises the amino acid sequence QMKDIFYSLLASLAA.

5 233. A pharmaceutical composition comprising a amino acid sequence which binds specifically to IR receptor at Site 1 and is an insulin agonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof, and a pharmaceutically acceptable carrier.

10 234. The pharmaceutical composition according to claim 233, wherein the peptide comprises the amino acid sequence FYDWF.

235. The pharmaceutical composition according to claim 233, wherein the peptide comprises the amino acid sequence FYSLLASL.

15 236. A method of treating diabetes comprising administering to an individual in need of treatment a therapeutically effective amount of an amino acid sequence which binds IR at Site 1 and is an insulin agonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.

237. The method according to claim 236 wherein the amino acid sequence is expressed by a recombinant vector administered to the individual.

20 238. The method according to claim 236 wherein the amino acid sequence is administered to the individual as a polypeptide.

239. A method of treating a patient with an IGF sensitive tumor comprising administering to an individual in need of treatment a therapeutically effective amount of an amino acid sequence which is an IGF-1R antagonist, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.

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240. The method according to claim 239 wherein the amino acid sequence is expressed by a recombinant vector administered to the individual.

241. The method according to claim 239 wherein the amino acid sequence is administered to the individual as a polypeptide.

10 242. A method of screening for a compound which binds to IR comprising:

- i) immobilizing IR, or a fragment thereof, on a surface;
- ii) incubating the IR, or fragment thereof, with a known amount of labeled amino acid sequence of Formulas 1-10, or an amino acid sequence selected from Figures 10-11, which binds IR and a compound to be screened under conditions which provide for binding of the labeled amino acid sequence to IR;
- 15 iii) measuring the amount of labeled amino acid sequence bound to IR;
- iv) determining from the amount of bound labeled peptide whether the compound has competitively bound to IR.

20 243. An amino acid sequence capable of binding to Site 1 or Site 2 of IR identified by the method according to claim 242, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.

244. The amino acid sequence according to claim 243 wherein the amino acid sequence is an IR agonist.

245. The amino acid sequence according to claim 243 wherein the amino sequence binds to Site 1 of IR.

246. The amino acid sequence according to claim 243 wherein the amino sequence binds to Site 2 of IR.

5 247. A method of screening for a compound which binds to IGF-1R comprising:

- i) immobilizing IGF-1R, or a fragment thereof, on a surface;
- ii) incubating the IGF-1R, or fragment thereof, with a known amount of labeled amino acid sequence of Formulas 1-9, or an amino acid sequence selected from Figure 10, which binds IGF-1R and a compound to be screened under 10 conditions which provide for binding of the labeled amino acid sequence to bind to IGF-1R;
- iii) measuring the amount of labeled amino acid sequence bound to IGF-1R;
- iv) determining from the amount of bound labeled peptide 15 whether the compound has competitively bound to IGF-1R.

248. An amino acid sequence capable of bind to Site 1 or Site 2 of IGF-1R identified by the method according to claim 247, with the proviso that the amino acid sequence is not insulin, IGF, or fragments thereof.

249. The amino acid sequence according to claim 248 wherein the amino acid 20 sequence is an IGF agonist.

250. The amino acid sequence according to claim 248 wherein the amino sequence binds to Site 1 of IGF-1R.

251. The amino acid sequence according to claim 248 wherein the amino sequence binds to Site 2 of IGF-1R.

252. An amino acid sequence comprising the sequence  $WX_{123}GYX_{124}WX_{125}X_{126}$  wherein  $X_{123}$  is proline, glycine, serine, arginine, alanine or leucine,  $X_{124}$  is any amino acid;  $X_{125}$  is a hydrophobic amino acid; and  $X_{126}$  is any amino acid.

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253. The amino acid sequence according to claim 252 wherein  $X_{123}$  is proline and  $X_{125}$  is leucine or phenylalanine.

254. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 1.

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255. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 2.

256. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 3.

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257. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 4.

258. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 5.

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259. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 6.

260. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 7.
261. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 8.
- 5 262. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 9.
263. A recombinant peptide library comprising members wherein the majority of the members comprise an amino acid sequence of Formula 10.